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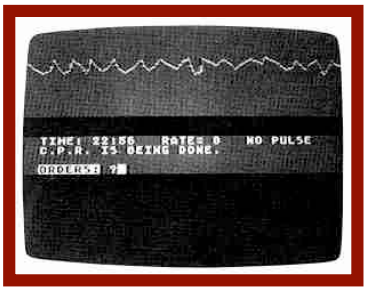
CRITICAL TIMES



A q-o-monthly Newsletter Issue No.VI Feels like Fall, 2010

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Sweet Success

I suppose one could create a medical joke along the lines of "how many people does it take to control a patient's blood sugar?" With changes in endogenous and catechols, dietary status, infections, and solid organ function in constant flux, and with only intermittent testing, it's a wonder that we can even maintain crudely acceptable values of blood glucose. Unfortunately, prevention of morbidity and mortality requires a greater ability to control spikes and troughs in blood sugar. Ideally, we would have the equivalent of an arterial line that displays current values in real time and allows one to adjust controlling medications with instant feedback. Since we do not possess that type of capability at present, all of our interventions are derived from response algorithms based on intermittent sampling. To make matters even more complex, the actual targets for therapy have moved around quite a bit in the last five years! So while the answer to the riddle should be 'zero' or 'one', in reality, it takes a whole team. In this issue, we hear from the folks who are routinely called in to help control glucose, manage the overall program, and provide information that helps us make reasonable decisions regarding glycemic control. Juli Barr will provide the rationale and evidence for improved glucose control, Bobette Nicholl will discuss recent changes in the MSICU glycemic control protocol, Mylinh Ho will discuss the kinetics and use of newer insulin analogs that may be able to help in the cause, and finally, Endocrinologists Drs. Kim and McLaughlin will provide some practical advice on managing some of the more resistant cases, and transitioning off of insulin infusions.

To continue on the theme of interdisciplinary teamwork, we will also hear from the new **Acute Pain Management Group** and the **Palliative Care Service** about their contributions to the care of the critically ill, and how to best engage these consultants in a productive manner.

In the issue to follow, I would like to consider the topic of education of both trainees and experienced providers and deal with questions such as how the different professions keep up on their fields, how new skills are learned, and how is competence achieved and evaluated. The changing time restrictions for resident training will be discussed as well as implications for the development of expertise in critical care. Any articles pertaining to these general themes would be especially welcome. For now, happy reading!

Geoff Lighthall, PhD, MD Editor

Glycemic Control in ICU Patients: Finding the Ideal Blood Glucose Range

Juli Barr, MD, FCCM

Hyperglycemia in Critically Ill Patients: Hyperglycemia occurs commonly in critically ill patients, regardless of whether they have a preexisting history of diabetes. This so called "stress-induced hyperglycemia" is a consequence of many factors, including increased circulating levels of cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis as part of the physiologic stress response.[i] Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80 percent of critically ill patients.[ii] Until recently, stress hyperglycemia was considered an adaptive response, providing a ready source of fuel during a time of increased demand. However, both short-term and long-term hyperglycemia are now recognized as having significant deleterious effects. Hyperglycemia increases oxidative injury, potentiates the pro-inflammatory response, promotes clotting, causes abnormal vascular reactivity, and impairs leukocyte and mononuclear cell immune responsiveness.[iii,iv] Stress hyperglycemia (BG >180 - 200 mg/dL) is associated with worse clinical outcomes in patients following acute myocardial infarction, stroke, and cardiac surgery, and in patients with congestive heart failure.[v,vi,vii,viii,ix] Trauma patients who are hyperglycemic, either on admission or during their ICU stay, have an increased mortality rate, hospital length of stay, ICU length of stay, and incidence of nosocomial infection.[x,xi,xii] Hyperglycemia is also associated with worse neurologic outcomes and increased intracranial pressure in patients with traumatic brain injury.[xiii] In general, critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate than ICU patients who are normoglycemic.[xiv] The higher the glucose levels in these patients, the higher the mortality risk. In a study by Falciglia, *et al* of 259,040 patients admitted to 173 medical, surgical, and cardiac ICUs, compared with normoglycemic individuals (70-110 mg/dL), adjusted odds of mortality (odds ratio, [95% confidence interval]) for mean BG levels ranging from 111-145 mg/dL, 146-199 mg/dL, 200-300 mg/dL, and>300 mg/dL was 1.31 (1.26-1.36), 1.82 (1.74-1.90), 2.13 (2.03-2.25), and 2.85 (2.58-3.14), respectively.[xv]

Glycemic Control in ICU Patients: Prior to 2001, stress hyperglycemia was defined as a plasma glucose above 180 mg/dL. In 2001, Van den Berghe and colleagues published the results of their single center trial (the Leuven Surgical Trial) where they randomly assigned 1,548 surgical ICU patients (primarily cardiac surgery patients) to receive intensive insulin therapy (IIT) or conventional blood glucose management.[xvi] IIT was defined as an

insulin infusion targeting a blood glucose range of 80 to 110 mg/dL. Conventional blood glucose management targeted a blood glucose range of 180 to 200 mg/dL, and used an insulin infusion only if the blood glucose was greater than 215 mg/dL.

1. ICU mortality was significantly lower in the IIT group (4.6% vs. 8.0% in the control group), with the greatest benefit observed amongst patients who were in the ICU for $\geq$ 5d.
1. Hospital mortality was significantly lower in the IIT group (7.2% vs. 10.9% in the control group).
2. IIT was associated with a lower incidence of critical illness poly-myoneuropathy and acute renal failure, lower transfusion requirements, and a lower incidence of blood stream infections.

In 2006, Van den Berghe and colleagues repeated the Leuven study design in medical ICU patients.[xvii] Patients in this study who were randomized to the tight glycemic control group demonstrated a significant reduction in morbidity. Although the results in this study failed to reproduce the improvement in survival observed in the previous Leuven study of surgical patients, there was a significant reduction in mortality observed in the subset of medical ICU patients with an ICU length of stay of $\geq$3 days.

In 2009, the results of the multicenter Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial were published.[xviii] The largest ICU glycemic control study to date, this study randomly assigned 6,104 medical *and* surgical ICU patients to receive either IIT (target blood glucose level of 81 to 108 mg/dL) or conventional glucose control (target blood glucose of <180 mg/dL). Although the conventional glucose control group was defined only by a maximal blood glucose target, the insulin infusion was reduced and then discontinued if the blood glucose level dropped below 144 mg/dL. Compared to the conventional glucose control group in this study:

1. The IIT group had a significantly lower time-weighted blood glucose (115 vs. 144 mg/dL).
2. The IIT group had a significantly higher 90 day mortality (27.5% vs. 24.9%, OR = 1.14, 95% CI = 1.02-1.28).
3. The IIT group had a significantly higher incidence of severe hypoglycemia (6.8% vs. 0.5%), defined as a blood glucose <40 mg/dL.
4. In the subgroup of 2,232 operative patients, those patients who received IIT had a significantly higher mortality than those who received conventional glycemic control (24.4% vs. 19.8%, OR = 1.31, 95% = CI 1.07-1.61).

However, there were important methodological differences between NICE-SUGAR study and original work by Van den Berghe's study in 2000, including: different target ranges for BG levels in the control groups for each study; significant overlap between the treatment groups in the NICE study; and variation in the accuracy of BG monitors, sampling site, and infusion pumps used in the NICE study.[xix,xx]

In 2009, Griesdale and colleagues published the results of a meta-analysis of 26 ICU glycemic control studies (including data from the NICE-SUGAR study), which included 13,567 adult medical and surgical ICU patients, to determine the influence of intensive insulin therapy (IIT) (target BG $\leq$ 150 mg/dL) compared with conventional insulin therapy (target BG < 180 mg/dL) on the risks of mortality and severe hypoglycemia ($\leq$40 mg/dL) in ICU patients.[xxi] Of the 26 studies included in this meta-analysis, 6 were conducted in medical ICUs (1,460 patients), 5 in surgical ICUs (1,972 patients), and 15 in mixed medical-surgical ICUs (10,140 patients). The results of this meta-analysis demonstrated:

1. The pooled analysis of all 13,576 ICU patients showed no difference in mortality risk between IIT and conventional insulin therapy (RR = 0.93, 95% CI = 0.83–1.04).
2. Patients in surgical ICUs appeared to benefit from intensive insulin therapy

in terms of mortality risk (RR 0.63, 95% CI 0.44–0.91), while patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI = 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12).

3. Among the 14 trials that reported hypoglycemia, the pooled RR with intensive insulin therapy was 6.0 (95% CI = 4.5–8.0).

4. Differences in targets of intensive insulin therapy between studies (BG $\leq$ 110 mg/dL vs. BG $\leq$ 150 mg/dL) did not influence either mortality risk or the risk of hypoglycemia.

More recently, Marik and Preiser published the results of a meta-analysis of all 7 studies of tight glycemic control, which included 11,425 adult medical and surgical ICU patients targeting a BG = 80 - 110 mg/dL.[xxii] This systematic review looked at the mortality benefit of tight glycemic control in the ICU setting, and attempted to explain differences in the treatment effect among studies by meta-regression. Unlike previous meta-analyses, this study *only* included randomized controlled trials (RCTs) that specifically attempted to confirm the benefits of IIT (BG = 80-110 mg/dL) as compared with less strict glycemic control in ICU patients. The results of this meta-analysis showed that:

1. Overall, ITT did not reduce the 28-day mortality (OR = 0.95; 95% CI, 0.87-1.05).

2. ITT did not reduce the incidence of blood stream infections (OR 1.04; 95% CI, 0.93-1.17), or the requirement for renal replacement therapy (OR 1.01; 95% CI, 0.89-1.13).

3. The incidence of hypoglycemia was significantly higher in patients randomized to tight glycemic control (OR 7.7; 95% CI, 6.0-9.9; P , .001).

4. Meta-regression demonstrated a significant relationship between the treatment effect (28-day mortality) and the proportion of calories provided parenterally (*P* = .005). This suggests that the difference in outcome between the two Leuven Intensive Insulin Therapy Trials and the subsequent trials could be related to the use of parenteral nutrition.

5. When the two Leuven Intensive Insulin Therapy Trials were excluded from the meta-analysis, mortality was lower in the control patients (OR = 0.90; 95% CI, 0.81-0.99; *P* = .04).

The authors of this meta-analysis noted that these results do not necessarily apply to more moderate approaches to glycemic control (blood glucose targets > 110 mg/dL but < 180 mg/dL).

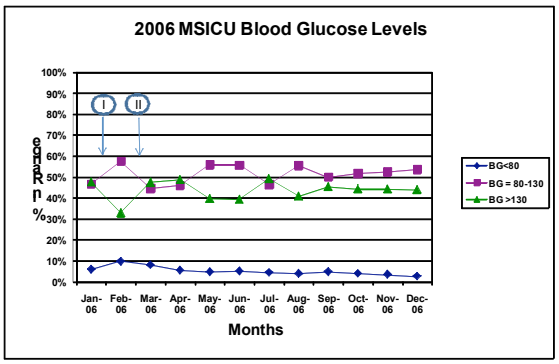
Hypoglycemia is the most common adverse effect of IIT. It occurs in up to 19% of ICU patients when defined as a blood glucose <40 mg/dL, or up to 32% of ICU patients when defined as a blood glucose <60 mg/dL.[xxiii,xxiv] Its frequent occurrence is problematic because hypoglycemia can lead to seizures, brain damage, depression, and cardiac arrhythmias.[xxv,xxvi,xxvii,xxviii] Hypoglycemia is also an independent risk factor for death in ICU patients.[26,28,xxix]

It remains unclear as to what the ideal blood glucose range is in order to optimize clinical outcomes in ICU patients. To date, the majority of studies have looked at the effects of tight glycemic control (i.e., maintaining BG between 80 - 110 mg/dL) on morbidity and mortality in these patients. Maintaining BG levels < 110 mg/dL is associated with a high incidence of hypoglycemia, while maintaining BG levels between 110 - 200 mg/dL increases the risk of death in ICU patients by approximately 30 - 80%.[15,24,25] More studies are needed to assess the relative risks and benefits of more modest glycemic control in critically ill patients. A joint statement recently released by the American Association of Clinical Endocrinologists and the American Diabetes Association suggests that "*it would be a serious error to conclude that judicious control of glycemia in critically ill patients, and in non-ICU patients in general, is not warranted*." Furthermore, they suggest that "*perhaps major beneficial effects on outcomes can be derived from a higher target range of glucose than 80-110 mg/dL in comparison with uncontrolled hyperglycemia*," recommending that the blood glucose

level be maintained between 140 and 180 mg/dL in these patients.[xxx] Based on the results of the recent meta-analysis by Griesdale, *et al*, surgical patients may benefit from tighter glycemic control, maintaining BG levels < 150 mg/dL.[22]

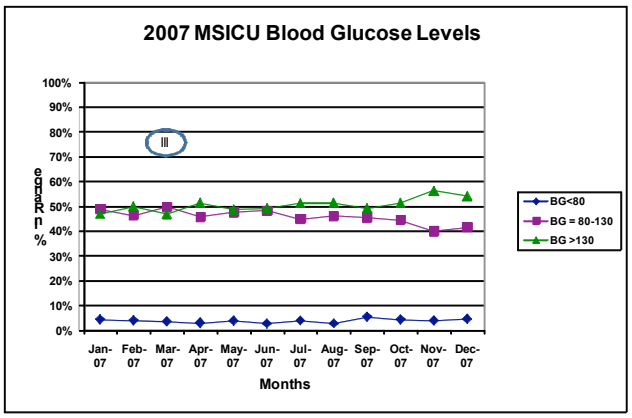
Glycemic Control in ICU Patients admitted to the MSICU: In February 2006, in response to a growing body of evidence at that time demonstrating the beneficial effects of tight glycemic control on clinical outcomes in ICU patients, a glycemic control protocol (GCP) was implemented and applied to all patients admitted to the MSICU. The goal of this protocol was to maintain a target BG range of 80 - 130 mg/dL in all medical and surgical ICU patients who were not eating (i.e., those who were either NPO, or on continuous enteral or parenteral nutrition). All patients had a baseline BG checked upon admission to the MSICU. For those patients who were not taking oral nutrition, if their BG level was > 130 mg/dL, they were placed on an IV insulin infusion to target a BG = 80 - 130 mg/dL. Blood glucose levels were checked in these patients every 1 - 2 hours. Patients who were able to take po nutrition normally were placed on either oral hypoglycemic agents, and/or a Q6 hr prn SS SQ insulin regimen to keep their BG < 200 mg/dL, with BG levels checked Q6 hr. This protocol was incorporated into an order set in the CPRS system.

During the first month following implementation of Phase I of the GCP protocol, compared to the previous month, mean BG levels in ICU patients decreased from 140 to 124 mg/dL, but the incidence of hypoglycemia increased from 5.9% to 9.8%.(Figure 1).

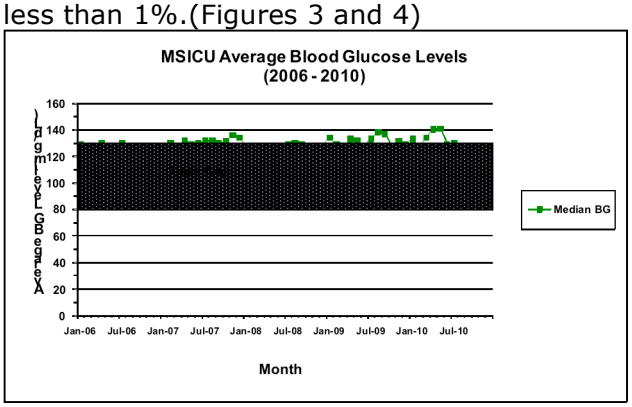


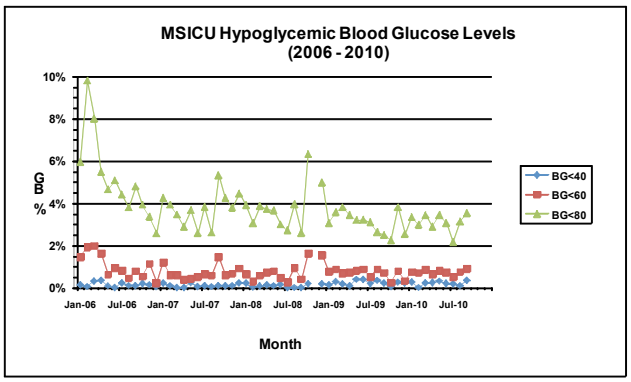
At the end of March 2006, the insulin infusion regimen used in the protocol was relaxed somewhat, and Phase II of the GCP protocol was implemented. This was followed by a steady decline in hypoglycemic events, and by December 2006, the incidence of hypoglycemia had decreased to only 2.6%, which was lower that the our baseline incidence of hypoglycemia in MSICU patients.

After conducting a GCP compliance audit of nursing practice in the MSICU in June 2006, we realized that much of the observed improvement in ICU glucose control was the result of ICU nurses deviating significantly from the written protocol, in an effort to tailor insulin drip titrations to patients based upon their individual need for insulin, rather than based upon a universally rigid protocol that specified insulin infusion rates for specific BG levels. After extensive discussions with the MSICU nursing staff and Pharmacy Service, along with input from outside experts in this field, the ICU GCP protocol was further modified to allow nurses more flexibility in adjusting insulin infusions in response to changes in BG levels in individual patients. In March 2007, Phase III of the GCP protocol was implemented.(see Appendix on line) This version of the protocol allows ICU nurses to tailor adjustments in the insulin infusion in response to BG levels in individual ICU patients, much like they do with vasoactive, sedative, and analgesic infusions in the ICU (i.e., Titrate the IV insulin infusion rate between 0-10 units/hr to maintain target BG = 80- 130 mg/dL).(Figure 2)



This protocol limits the incremental increases in the insulin infusion rate by no more than 4 units/hr, and mandates that BG levels are checked every 1-2 hours until the target BG is achieved for 2 or more consecutive BG checks. Then BG levels are checked every 4 hours thereafter until the IV insulin infusion is D/Ced. The protocol also provides nurses and physicians with cautionary notes about subpopulations of ICU patients who are at higher risk for developing hypoglycemia on an insulin infusion (i.e., renal failure and end-stage liver disease patients, etc.). This approach has enabled us to achieve tight glycemic control while minimizing the incidence of hypoglycemia in our patients. Between February 2006 and September 2010, the median monthly BG levels in MSICU patients has been 129 mg/dL, while the overall incidence of moderate hypoglycemia (<60 mg/dL) is less than 1%.(Figures 3 and 4)





However, in light of recent evidence showing that there is no clear benefit to maintaining BG levels this low, and given the labor intensity of GCP by the ICU nursing staff, we are now considering making additional modifications to our existing ICU glycemic control protocol, possibly expanding the target BG range to 80 - 150 mg/dL.

We also continue to face challenges in maintaining adequate BG control in patients who are not receiving insulin infusions in our ICU. In spite of recent efforts by the Pharmacy Service to eliminate the use of "mild" SS insulin regimens in ICU patients (which resulted in no insulin being administered for BG < 200 mg/dL), and with low carb alterations in the standard diet regimens for all ICU patients taking oral nutrition, we continue to have many ICU patients, especially cardiac surgery patients, with recurrent or persistent hyperglycemia (BG > 200 mg/dL). From the literature, we know that this can potentially result in bad clinical outcomes for these patients. More needs to be done as well to improve glycemic control in ICU patients taking po who are not presently being managed with an insulin infusion.

In the coming weeks, we will be working closely with the ICU Nursing Staff, ICU Physicians, Pharmacy Service, Dietary Service, Surgical Service, and staff Endocrinologists to further modify and improve our glycemic control protocol in the MSICU. Your input will be appreciated!

NOTE: references for Dr. Barr's article can be found on the last page of the newsletter

The Glycemic Control Protocol

Bobette Nicholl, RN
Nurse Manager, MSICU

The MSICU first implemented the Glycemic Control Protocol in 2006 with input from the ICU nursing staff and Attending physicians. We have gone through several revisions of the protocol since that time based on staff suggestions and a glycemic control survey which tested nursing knowledge and basic understanding of the protocol.

The target glucose range for all ICU patients is 80-130mg/dl. A recent review of mean BG levels performed in the ICU from 2006-2010 demonstrated a high percentage of mean BG levels above the target range. The CT surgeons have been very interested in maintaining appropriate glucose levels in their patients in order to prevent surgical site infections. The ICU is accountable for a Performance Measure whereby all cardiovascular patients MUST have a glucose <200mg/dl at 6am on POD#1 And POD#2. Our benchmark was 92% compliance; however, the ICU has failed this measure for FY 2010. Barriers to our success included increased patient acuities, loss of nursing assistant support with glucometer testing, resistance from fellows/residents to order aggressive insulin scale, and patients with multiple infusions containing D5W contributing to high glucose levels.

As a team, we are now aggressively addressing this issue. We have made several significant improvements in our care of diabetic patients including:

- review of data addressing mean BG levels during staff nurse meetings
- conversion of IV infusions (including insulin) to NS instead of D5W, when possible
- sugar-free juices/snacks now available to ICU patients
- dietary change for all cardiovascular patients to 1600-1800 low carb meals
- insulin infusions for patients taking PO who are uncontrolled on SS insulin
- ICU Attendings educating/reiterating glycemic protocol to fellows and residents
- elimination of the "mild" insulin sliding scale

The next step in our improvement plan will be a "stakeholders" meeting that includes ICU staff nurses, nurse manager, CT surgeon, ICU Attending, Chief of Endocrinology, and pharmacy. Maintaining proper mean glucose levels in our ICU patients is within our grasp!

We appreciate all your suggestions and continued support.

Insulin Analogues

Mylinh Ho, Pharm.D., BCPS

Insulin analogues have been modified to enhance their pharmacokinetic profile to create advantages over standard human insulin. In addition to our current armamentarium of regular and NPH insulin we now have access to an expanding repertoire of agents which include rapid-acting, pre-mixed biphasic and long-acting analogues. Zinc atoms are added to a solution of dimers that make up regular insulin, thus forming larger molecules (hexamers). After subcutaneous injection, the rate at which these polymers dissociate into absorbable monomers determines insulin's onset of action. With regular insulin, onset can take up to 30+ minutes, peak effect can be further delayed, and duration of action can become prolonged.

Rapid-acting Insulin Analogues

The three rapid-acting insulin analogues lispro, aspart and glargine have been structurally modified and rapidly dissociate into the active monomeric form resulting in 15 minutes onset of activity, peak action in 30-90 minutes and duration of 3-4 hours. This allows patients to lower their 2-hour postprandial blood glucose while reducing postprandial and night time hypoglycemia. Studies comparing rapid-acting analogues to regular insulin in patients on multiple daily injection regimens have not shown superiority in long term glycemic control, however, the incidence of severe hypoglycemia was lower.

Biphasic Insulin Analogues

Biphasic insulin analogues are premixed products designed to provide a relatively longer acting background level of insulin in combination with a rapid-acting analog. Insulin **aspart** or **lispro** are co-crystallised with protamine and the rate of absorption is slowed down similar to that of NPH. Aspart comes as a 70% aspart protamine suspension, 30% aspart and lispro as either 75% neutral protamine lispro, 25% lispro or 50% neutral protamine lispro, 50% lispro.

The main disadvantages of these products are the fixed dose regimen, which provides little flexibility and lack of pre-lunch time coverage which would potentially require that the patient inject a separate dose of rapid-acting insulin. Premixed products can be considered in patients who have difficulty with self monitoring and adherance.

Long-acting Insulin Analogues

Traditionally neutral protamine hagedorn (**NPH**) insulin given subcutaneously has been used to achieve a background or basal level of insulin. NPH's variable absorption (varies with site of injection, exercise, body temperature), inconsistent mixing/preparation of the product and inherent pharmacokinetic profile can make glucose control labile.

Insulin **glargine** provides a peakless insulin profile with duration of action close to 24 hours; this is done by changing its isoelectric point, or pH at which insulin is least soluble and precipitates. Glargine's pH is acidic at 4.0 and when injected into the neutral pH of subcutaneous tissue, it precipitates and forms a depot which slowly releases. Glargine should not be mixed with any other insulins as that can change its pH and time-action profile.

Insulin **detemir** is long-acting by addition of a fatty acid side chain to its insulin molecule which binds to interstitial albumin at the SQ injection site. Its dissociation from albumin can be prolonged, given its hexameric structure. Once it enters into circulation, detemir binds to albumin and travels to insulin receptors where it dissociates and exerts its action. Detemir peaks at 14-18 hours but can be further delayed with higher dosing regimens. Relatively higher doses also prolong duration of action close to 24 hours.

Efficacy of long term glycemic control with these analogues has been shown to be comparable to that of NPH but these products cause less nocturnal hypoglycemia. Long-acting insulin analogues would benefit patients who experience recurrent nocturnal hypoglycemia or need assistance consistently mixing and preparing NPH.

Pharmacokinetic Profiles of Various Insulins

Type of insulin	Onset	Peak (hours)	Duration (hours)	Max Duration (hours)
Rapid-acting				
Lispro (Humalog)	15-30min	1-2	3-4	4-6
Aspart (Novolog)	15-30min	1-2	3-5	5-6
Glulisine (Apidra)	15-30min	1-2	3-4	5-6
Short-acting				
Regular; human, rDNA (Humulin R, Novolin R)	30-60min	2-3	3-6	6-8
Intermediate-acting				
NPH	2-4 hours	4-6	8-12	14-18
Premixed		30-60min	2-12	14-18
Reg/NPH (Humulin) 30/70	*these times apply to all premixed product*			
Reg/NPH (Novolin) 30/70				
40/60				
50/50				
Lispro/protamine lispro (Humalog Mix)				
25/75				
50/50				
Aspart/protamine aspart (Novolog Mix)				
30/70 Pharmacokinetics similar to rapid-acting + NPH				
Long –acting				
Detemir (Levemir)	2 hours	6-9	14-24	24
Glargine (Lantus)	4-5 hours	--	22-24	24

Usefulness of Insulin Analogues in the ICU

In the ICU, continuous intravenous infusions of insulin are commonly used to provide tight glycemic control. Though rapid-acting insulin (aspart, lispro) may safely be used intravenously instead of regular human insulin, there is no benefit to doing this and it is significantly more costly. Long-acting insulin analogues (glargine, detemir) should never be used IV, as profound hypoglycemia may occur.

When transitioning diabetic patients to oral/enteral diets, SQ rapid-acting insulin may be used for corrective replacement scales or as pre-prandial doses along with intermediate or long-acting insulin. When patients are consuming consistent meals or stable tube feed diets, twice daily NPH may be added. Glargine/detemir may be used if side effects of nocturnal or severe hypoglycemia are experienced with NPH.

The majority of pharmacokinetic data about insulin analogues are obtained from otherwise healthy diabetic volunteers. There are many factors in critically ill patients that can cause significant variation in insulin absorption and clearance including hypoperfusion, edema, hepatic and renal insufficiency. In critically ill patients, it is important to monitor blood glucose frequently, at least QID, to optimize efficacy and to detect hypoglycemia early.

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Endocrine Corner:

Some thoughts about insulin drips for management of hyperglycemia in critically-ill patients

Sun Kim, M.D., M.S.
Tracey McLaughlin, M.D., M.S

Although insulin drips can add extra work for the care team, it is the most effective means to control glucose concentration in critically-ill patients with hyperglycemia.

1. What is the glucose target in critically-ill patients?

140-180 mg/dL Although controversy exists about target glucose levels in hospitalized patients, there is good evidence that patients with hyperglycemia have worse clinical outcomes including higher mortality. In recent clinical trials (e.g., NICE-SUGAR), lower glucose targets increased risk for hypoglycemia and possibly mortality, leading to the change in target from 110 to the current target of 140-180 mg/dL.

2. How do you assess readiness to transition off an insulin drip?

In addition to clinical status, patients are ready to transition off of an insulin drip when glucose concentrations have been in a target range for 4 hours and the insulin drip rate has been stable (± 1 unit/hour) for 4 hours.

In order to attain a stable state, the patient cannot be receiving bolus/oral feeds of any kind. Continuous intravenous or tube feeds are allowed. If the patient is eating, hold food after the last meal until ready for transition – glucose can be given with intravenous fluids. Most patients will stabilize glucose and insulin hourly rate within 8-12 hours. Doing this after dinner and holding breakfast until team assesses glucose/insulin rates is ideal for transitioning patients who are eating and do not want to stop.

3. How do you transition off of an insulin drip?

In order to determine the subcutaneous insulin dose and regimen, there are three steps: (1) Estimate the total daily dose (TDD) of insulin that will be required. The TDD is estimated from the hourly rate of intravenous insulin when patients are stable and ready for transition (above). (2) Adjust TDD (aTDD) for anticipated lower needs due to decreasing level of illness. Take into account improving infection, lowering doses of pressors, and other decreasing physiological stressors. (3) Determine allocation of aTDD into basal and prandial insulin doses.

HOW TO DO THIS:

(1) TDD = final average <u>hourly</u> insulin drip rate (<u>average</u> of last 4 hours) X 24 hours

(2) Adjust TDD for anticipated decrease in physiologic stress:

• Adjusted TDD (aTDD) = 75% of calculated TDDd

(3) Allocate to basal and prandial (premeal insulin to cover food) insulin. See below.

a) <u>Determining "basal" insulin</u> (long acting, not for food, includes NPH, lantus, levemir): Most patients coming off of an insulin drip are **not eating (this is required for transition)** and therefore the aTDD can be allocated entirely to NPH split BID. For example, hourly drip rate is 2 units/hr. The TDD = 2 x 24 = 48 units; aTDD = 0.75 x 48 = 36 units. Patient is not eating. Subcutaneous insulin dose is 18 units of NPH BID.

b) <u>Adding prandial insulin</u> (rapid acting, to cover food, includes aspart, lispro, regular insulin): As the patient begins to eat, prandial insulin is added. To do this, small fixed doses of aspart or lispro are ordered qAC. Start with 2-3 units and eventually work up to a total daily dose of prandial insulin that is equal to the total dose of basal insulin (NPH).

c) <u>Which basal and prandial insulin to use</u>: Basal: start with NPH split BID, then can switch to lantus once doses are not changing for several days. This is because the effect of NPH can be seen immediately. NPH also has a shorter half life and is better for unstable patients whose doses are expected to change daily. Prandial: use aspart or lispro. Regular insulin is discouraged unless the patient has gastroparesis or is on continuous feeds (e.g., tube feeds or TPN).

d) <u>Switching from NPH to lantus</u>: Note that once stable doses of NPH are reached (usually after transfer out of ICU – note that as patient gets well, doses may decrease) NPH total daily dose can be converted to lantus, once daily (or levemir split BID).

e) <u>Tube feeds</u>: If patient is receiving continuous tube feeds, the aTDD will be split 50/50 between NPH and prandial insulin. For aTDD of 36 units, 18 units will be given as NPH, split q6hrs while on continuous tube feeds. The other 18 units will be given as regular insulin, given q6hrs while on continuous tube feeds.

f) <u>TPN</u>: If patient is receiving TPN, the aTDD will be split 50/50 and half given as NPH split BID or q6 hours, and the other half added to the TPN bag. For TPN, regular insulin can be used in place of lispro or aspart as the action profile of intravenous regular insulin is similar to lispro or aspart.

g) <u>What about sliding scale</u>? Always order sliding scale in addition to the standing orders of insulin. Sliding scale should be viewed as the "icing on the cake" rather than the mainstay of insulin treatment. Use the same type of insulin (lispro, aspart, regular) as ordered for the fixed prandial doses and dose on the same schedule (qAC and HS, or q6hrs). Be sure glucometer finger sticks are ordered on this same schedule as well.

h) <u>Daily adjustments</u>: Adjust fixed doses of basal (NPH) and prandial (lispro, aspart, regular) insulin every day according to the total amount of insulin required. For example, if NPH was 9 units BID and prandial aspart was 6 units qAC for a total dose of 36 but an additional 12 units of aspart were given by sliding scale, the new TDD of insulin is 48 units. Therefore, the fixed doses should be increased to a total of 48 units as follows: NPH 12 units BID and prandial aspart 8

units qAC (OR 6units q6 hrs if on continuous tube feeds OR 24 units total in TPN bag). Continue sliding scale.

i) Which sliding scale to use: The proper scale depends on the TDD of insulin. Rule of thumb: Divide TDD into 1700. The result is the mg/dL increment drop in glucose that will result from 1 units of insulin given by sliding scale. The scale should reflect similar increments. For example, TDD=36. 1700 divided by 36 = 47. Thus one unit of insulin will drop glucose by 47 mg/dL. Scale should increase in increments of approximately 47 mg/dL (round to 50). So 151-200 add 1 unit; 201-250 add 2 units, etc.

The ICU and Palliative Care – Working Together to Deliver Quality Care to Veterans and Their Families.

Michelle S. Gabriel, RN, MS
Jim Hallenbeck, MD

Got Palliative Care? Whenever you are helping a Veteran who is suffering with pain, dyspnea, or some other troubling problem, whenever you console or support a stressed family member, congratulations! You are delivering palliative care. But when might a palliative care consult be helpful? If a Veteran with metastatic pancreatic cancer is septic, doing poorly, and the family says, "Enough is enough," then a palliative care consult would probably be very appropriate. However, the palliative care consultation service can be helpful in other situations as well.

Here are 4 examples of when you might want to consider involving palliative care beyond referral of a patient with a terminal condition:

1. The veteran is experiencing unusual or unrelieved symptoms. Palliative care clinicians specialize in symptom management. From pain management to constipation, anxiety to dyspnea, palliative care clinicians are up to date on the management of distressing symptoms and may be able to offer suggestions for therapies not previously considered.

2. The team could use some help in discussing prognosis or care options beyond the ICU. Palliative care clinicians may help with prognostication, but not just in terms of whether a patient will live or die. They may help providers, Veterans and their families strategize care options for when the patient leaves the ICU. This can be particularly important when a major decline has occurred in a patient's health or functional status and the patient will need ongoing support. This may include a "goals of care" discussion, but may also involve very practical advice on benefits and living options beyond the acute care hospital.

3. Disputes and tensions arise. Caring for seriously ill patients in the ICU is hard work and stressful for everybody. When things heat up, sometimes it is useful to get help from an outside team with special communication and negotiation skills. While the primary mission of palliative care is the help of patients and families, palliative care is also there to support ICU staff, who also may be struggling with a difficult case.

4. When you are just not sure. Sometimes, uncertainty itself is a good trigger – at least for an informal curbside from a palliative care colleague to see if palliative care might have something to offer. Curbsides happen all the time for other specialties and may be helpful from palliative care as well. Maybe all that is needed is quick advice on a particular drug dose or a question regarding whether a particular therapy might help. Help doesn't always have to take the form of a formal consult.

DID YOU KNOW?

- Palliative Medicine is now an official medical specialty, supported by 10 medical boards, including Internal Medicine, Anesthesia, Surgery, and Pediatrics.
- Our fellowship was one of the first programs in the country to become

ACGME accredited in hospice and palliative care. We have one of the largest and most respected training programs in the country.

• Palliative care is defined as, "That aspect of Medicine that works to relieve suffering and improve quality of life *REGARDLESS OF THE STAGE OF ILLNESS*," (National Consensus Guidelines 2003).

So, while palliative care often does help with the care of dying patients and may help transition patients to hospice, hospice and palliative care are not really the same thing. Palliative care is not just for the dying. Palliative care, whether delivered by ICU staff or a specialist team, should be a component of *all* good medical care.

Postoperative analgesia for the ICU patient

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Director, Regional Anesthesia and Perioperative Analgesia Service
Department of Anesthesia

In September 2010, the Regional Anesthesia and Perioperative Analgesia Service was created to serve our veterans with the highest level of pain management in the perioperative period. Members of this Service currently include regional anesthesia attendings and fellows. The purpose of the Service is to provide a comprehensive and multimodal approach to pain management. One effective modality for pain control in select patients is epidural infusions. Although the decision to place an epidural catheter is frequently made prior to surgery by the operating room (OR) anesthesia team, the management of epidural catheters inevitably extends beyond the OR. To provide continuity of care, members of this Service will round daily on patients with epidural catheters and communicate with the ICU, primary, and consulting teams to optimally manage epidural infusions.

There are many benefits of epidural analgesia but its risks should be carefully considered for each patient. ICU patients require a higher level of care and common side effects of epidural infusions can potentially encumber proper recovery. Continuous infusion of local anesthetic may lead to hemodynamic instability like hypotension while excess epidural opioids can cause respiratory depression and sedation. The insertion and removal of epidural catheters require vigilant inspection of coagulation status to minimize risk for spinal/epidural hematoma, a rare complication which can lead to spinal shock and potentially catastrophic neurologic outcomes.

Effective and safe management of epidural infusions requires clear communication among the ICU, primary, regional anesthesia, and consulting services. Because epidural infusions are intricately connected to a patient's intravascular volume status, circulatory homeostasis, and neurologic function, careful coordination among all the involved services is paramount. Although the overall coordination of services and point-of-care decisions will be managed by the ICU team, it is imperative that the Regional Anesthesia Service be informed of changes in the patient's status and treatment plans. To facilitate open communication and mutual understanding regarding epidural analgesia, members of the Regional Anesthesia Service will be available at all times, including nights and weekends.

The Regional Anesthesia and Perioperative Analgesia Service also performs ultrasound-guided peripheral nerve blocks (PNB) for perioperative pain control. The objective of PNB is to target a specific nerve or plexus to alleviate pain in a given region of the body. Advantages of PNB include lower systemic opioid requirements, reduced opioid-related side effects (nausea, sedation, constipation), faster recovery and increased participation

in rehabilitation, and decreased overall hospital stay. Currently, PNB are being performed here at the VAPA as single injections (duration 6-12 hrs depending on local anesthetic) but steps are being taken to implement continuous PNB. Continuous PNB consist of placing a perineural catheter for administration of local anesthetic by an infusion device. However, unlike epidural infusions, PNB achieve analgesia with local anesthetic only. A scenario for the ICU may be a patient s/p a motorcycle accident with a fractured humerus and femur requiring high opioid consumption. If indicated, continuous brachial plexus and femoral nerve catheters can be placed for improved analgesia. Likewise, patients may arrive to the ICU after surgery with continuous PNB catheters placed in the OR. As is the case with epidural infusions, patients with continuous PNB will also be rounded daily by the Service.

On behalf of the Regional Anesthesia and Perioperative Analgesia Service members, I look forward to working more closely with the ICU staff to offer our veteran patients quality perioperative analgesia.

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Below are the papers cited in Dr Barr's article on page 2

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